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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GAKH, YELENA G	

ART UNIT	PAPER NUMBER
1797	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/765,718	ISMAGILOV ET AL.	
	Examiner	Art Unit	
	Yelena G. Gakh, Ph.D.	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,11-15,17,19,21-30,34,36,38-44,49-62 and 75-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,11-15,17,19,21-30,34,36,38-44,49-62 and 75-77* is/are rejected.

7)☒ Claim(s) *76* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/19/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. RCE and amendment, filed on 09/19/08, are acknowledged. Claims 8, 10, 16, 18, 20, 31-33, 35, 37, 45-48 and 63-74 are cancelled. Claims 1-7, 9, 11-15, 17, 19, 21-30, 34, 36, 38-44, 49-62 and 75-77 are pending in the application and considered on merits.

Response to Amendment

2. In response to the amendment the examiner modifies rejections under 112, first and second paragraphs. Rejection over the prior art is maintained.

Claim Objections

3. Claim 76 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim recites simultaneous introduction of three plug- fluids, which is an inherent feature of the method of the parent claim, since without such simultaneous introduction no plugs, which contain all three fluids recited in claims 1 and 3, could be formed.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 1-7, 9, 11-15, 17, 19, 21-30, 34, 36, 38-44, 49-62 and 75-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method comprising: a) using microchannel, rather than any channel; and b) having the capillary number of the plug in the channel is low, typically less then 1, and most preferably ≤about 0.1, does not reasonably provide enablement for the method which lacks these features. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The instant disclosure specifically indicates

that the method requires, a) forming the plugs in the capillary (i.e. microchannel), since using a macrochannel can obviously lead to forming laminar flows from plug-fluids and the immiscible carrier fluid, rather than the plugs; and b) "the capillary number of the plug in the channel is low, typically less then 1, preferably ≤ about 0.2 and most preferably ≤ about 0.1" (page 3, lines 27-29). It would have been an undue experimentation for a person of ordinary skill in the art to perform the method recited in the claims under any other conditions, since forming plugs in capillary and having plugs with low capillary number appear to be crucial features for the instant method.

B. Claims 1-2, 4-7, 23, 26, 36, 38-40, 49-62 and 75-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method comprising applying pressure to the channels to induce a fluid flow in the substrate to form substantially identical plugs comprising a mixture of plug-fluid, does not reasonably provide enablement for the method which lacks these three features. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The instant disclosure specifically indicates that the method requires, "applying pressure to the first channel to induce a fluid flow in the substrate to form substantially identical plugs comprising a mixture of plug-fluids" (page 3, lines 19-20). It would have been an undue experimentation for a person of ordinary skill in the art to perform the method recited in the claims under any other condition, since applying pressure appears to be a crucial feature for the instant method.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. Claims 1-7, 9, 11-15, 17, 19, 21-30, 34, 36, 38-44, 49-62 and 75-77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "plug-fluids" is still unclear and ambiguous. The examiner suggests replacing it with the term "plug-forming fluids".

From the claims it is not clear, as to whether the plug-fluids are introduced continuously or discontinuously into the channels. The way the plug-fluids are introduced into the channels is an essential feature of the method, because it is important to know, whether the plugs can be formed in any case, or they can be formed only under the condition of a discontinuous introduction of the plug-fluids.

Further, from claim 3 it is not clear, as to how the first plug type can comprise a precipitant and a crystallization target, when none of these components are indicated as being present in one or more first plug-fluids. The same is true for the plugs of the second plug type. It appears that the plug content is defined without any association with the plug-forming fluids, which makes it unclear, as to how the plugs receive their content.

Claim 3 recites "the plug-forming region". While the Applicants referred to a definition of the plug-forming region in the specification:

> "The term "plug-forming region" refers to a junction between an inlet port and the first channel of a substrate according to the invention. Preferably, the fluid introduced into the inlet port is "incompatible" (i.e., immiscible) with the fluid in the first channel so that plugs of the fluid formed in the plug-forming region are entrained into the stream of fluid from the first channel." (Page 15, lines 22-26),

it does not seem that this definition is applicable to the recitation of claim 3, which refers the a *second* plug-forming region *within* the first channel, and to a *second* plug-forming region *within* the *second* channel. First, the junction between the inlet port and the first channel cannot be defined as the region *within* the channel. Second, there is only one junction between the inlet port and the first channel, and therefore it is not clear, as to how the second plug-forming region can exist within the same channel.

Claims 6 and 7 are unclear in two aspects. First, it is not apparent, as to which solvent is meant in claim 6, since claims 1 and 3 do not recite any solvent - rather, they recite plug-fluids, one of which comprises water. The recitation of claim 6 makes it unclear, as to whether it is water of the second fluid-plug which is considered to be a solvent transferable from one plug into another plug. If this is the case, then it becomes unapparent, as to which further limitation claim 7 recites into claim 6. On the other hand, if this is a solvent different from water, then it becomes unclear, as to which solvent this

might be, and how the recitation of claim 6, related to the permeability of the carrier-fluid to water, is relevant to the solvent transfer.

Furthermore, from claims 6, 38, 40, 44 and others reciting this limitation, it is not quite clear, as to what the term "permeable" might mean in regards to relation between two liquids. To the examiner's understanding, the term "permeability" is usually referred to a penetration of gases or fluids into the solid, or through a membrane or filter. Moreover, if the carrier fluid and water are essentially immiscible, it is not clear, how the carrier fluid can be permeable to water. Clarification is respectfully requested.

From claim 25 it is not apparent, as to what "indexing marker" might be. Is this a compound? What does it index?

From claims 27-30 it is not apparent, as to how the osmolarity of the plugs can be measured to meet the requirements recited in the claims. It is not clear, as to whether the osmolariy is defined by the corresponding plug-forming fluids.

Claim 49 recites "a marker", which is an unclear and indefinite term in regards to the subject matter of the parent claim, since it is not apparent, as to what it refers to.

From claim 52 it is not clear, as to whether "a capillary tube" is equivalent to the channel of the parent claim, or it means that the crystal is removed from the channel and is placed into the capillary tube, which makes this transformation doubtful, since it is difficult to place a crystal into the capillary tube, unless the sizes of the crystal and the capillary tube are adjusted correspondingly. The same is true for claim 57.

Claims 53-59 recite the subject matter, which seems to be irrelevant to the subject matter of the parent claim. It is not clear, as how the steps of placing the crystal into different laboratory glassware affects the steps of the method recited in the parent claim.

Claim 60 is not clear, as to what does it mean that "the substrate comprises a material which allows water evaporation from the plugs". This recitation is not a clear and unambiguous definition of the material. Does it mean that the material should be hydrophobic?

The limitation "the solvent" recited in claim 75 does not have an antecedent basis.

From claim 77 it is not clear, as to how two plugs formed from the fluids immiscible with the carrier fluid and separated by the carrier fluid can be merged.

B. Claims 1-9, 11-15, 17, 19, 21-30, 34, 36, 38-44, 49-62 and 75-77 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: mixing the first, second and the third plug-fluids in order to form plugs which comprise all three plug-fluids.

Claim Rejections - 35 USC § 103

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. **Claims 1-7, 9, 11-15, 17, 19, 21-22, 24-30, 34, 36, 38-44, 51-62 and 75-77** are rejected under 35 U.S.C. 103(a) as being unpatentable over Weigl et al. (US 6,409,832) (Weigl) in view of Chayen (J. Cryst. Growth, 1999), as evidenced by Shaw et al. (GB 2,097,692, IDS) (Shaw), Lemaitre et al. (WO 98/02237, IDS) (Lemaitre), Torkkeli et al. (Int. Conf. on Sensors and Actuators, 2001, IDS) Torkkeli).

Weigl discloses "protein crystallization in microfluidic structures" with "a protein samples and a solvent solution combined within a microfluidic channel having laminar flow characteristics which forms diffusion zones, providing for a well defined crystallization". Weigl discusses various types of protein crystallization, and emphasizes that microfluidic crystallization is extremely efficient for diffusion-based crystallization:

> "A T-Sensor-like structure, generally indicated at 10, is shown in FIG. 1 to demonstrate the principles of diffusion-based crystallization. A sample 12 containing dissolved protein, and a reagent 14 containing a variety of different solvents and salts, flow together in parallel within a channel 15 of T-Sensor 10. After establishing a laminar flow profile, the flow is significantly slowed or stopped. The various components of both streams 12, 14 will now diffuse into each other at a certain rate, depending on the size of the molecules within these streams, forming diffusion interface zones 16, 18 within channel 15 of device 10. This action establishes a concentration gradient in device 10, which allows for a very well defined crystallization. Solvent molecules from one stream can diffuse into a parallel stream containing a different solvent and particles. The change in solvent properties along diffusion interface zones 16, 18 can then induce crystallization or precipitation. Obviously, it is also possible to apply a temperature gradient to a microchannel, either across the channel or along its flow direction, and affect the precipitation characteristics this way. Microseeding would be another possibility with this device" (col. 11, lines 54-67 and col. 12, lines 1-8). The fluids are introduced with syringes (under controllable pressure) (col. 12, lines 45-67).

Weigl discloses continuous laminar flow with stopping the flow after establishing a laminar flow profile. Weigl does not specifically disclose crystallization in plugs formed by the plug-fluids comprising corresponding components (a crystallization target, a precipitant, etc.).

Chayen teaches "crystallization with oils: a new dimension in macromolecular crystal growth". In particular, Chayen discloses the following:

> "A series of microbatch experiments shown in Fig. 2 demonstrates how the application of oil can determine the contact area between the trial and its supporting vessel, thereby enabling the experimenter to monitor the nucleation and reduce or increase its level at will. The Figure illustrates three situations: (a) illustrates a drop dispensed into oil as performed by the normal microbatch procedure[4]; the drop forms a spherical shape, with just a small part of it touching the floor of the container; (b) represents a drop which has been dispensed directly onto the floor of the vial and then covered by a layer of oil; the drop spreads out and flattens over the floor of the container, occupying a larger area of contact. In Fig. 2c all contact between the solution of a crystallization trial and its supporting vessel is eliminated by suspending a crystallization drop between two oils of different densities: one of higher and the other of lower density than that of water and the common crystallizing agents. The two oils, high-density fluorinated silicone fluid (ρ 1.27 g/cm3, Merck catalogue no. 63026 2C) and low-density polydimethylsiloxane (ρ 0.92 g/cm3, Merck catalogue no. 63003 4P) are not miscible and the drop, which has a density value between those of the two oils, floats at the interface thereby not touching the container walls [24,25]. *The number of carboxypeptidase G2 (CG2) crystals produced by procedures (a) and (c) is significantly reduced and their size is larger (Fig. 2d) compared with those grown by procedure (b) where the drop has the largest contact area with its vessel* (Fig. 3c). Similar results have been obtained with thaumatin, lysozyme [24,25] and apocrustacyanin C2 [24]" (page 437, right column, page 438, left column).

Thus, Chayen demonstrates advantages of controlling crystallization in a microdroplet suspended in the oil. Also, preferences of performing various chemical reactions in droplets are evidenced by any of Shaw, Lemaitre or Torkkeli.

It would have been obvious for a person of ordinary skill in the art to modify Weigl's method of crystallization in microfluidic structures by performing crystallization in plugs instead of during stop-flow, because Chayen expressly demonstrates preferences of microbatch crystallization in droplets suspended in oil, which are similar to plugs separated by an immiscible carrier fluid in microfluidic channels. It would have been obvious to have various plug-fluids comprising different components required for performing crystallization in order to form plugs with different composition and obtain a plurality of crystallization conditions for further high-throughput screening; it would have been obvious for a routineer in the art to analyze crystals either directly from the

microchannels or by transferring the crystals into conventional vials used for crystallographic analysis, such as X-ray analysis.

Such embodiments as obtaining different concentrations of the crystallization components for high-throughput analysis is well known in the art, with an obvious modification of the instant method by varying the pressure and the flow rates of the plug-fluids.

8. **Claim 23** is rejected under 35 U.S.C. 103(a) as being unpatentable over Weigl in view of Chayen, as evidenced by any of Shaw, Lemaitre or Torkkeli, as applied to claims 1-7, 9, 11-15, 17, 19, 21-22, 24-30, 34, 36, 38-44, 51-62 and 75-77 above, and further in view of Bardell et al. (US 2001/0048900 A1) (Bardell).

While Weigl in view of Chayen do not specifically disclose turn in a channel for increasing mixing in the channel, Bardell discloses specifically such turns in channels for increasing mixing of the fluids in the channels, which makes it obvious for a person of ordinary skill in the art to modify Weigl -Chayen's method by introducing turns in channels for increasing the mixing within the plugs.

9. **Claims 49-50** are rejected under 35 U.S.C. 103(a) as being unpatentable over Weigl in view of Chayen, as evidenced by any of Shaw, Lemaitre or Torkkeli, as applied to claims 1-7, 9, 11-15, 17, 19, 21-22, 24-30, 34, 36, 38-44, 51-62 and 75-77 above, and further in view of Pantoliano et al. (US 6,569,631) (Pantoliano).

While Weigl in view of Chayen do not specifically disclose fluorescent marker within one of the plug-fluids, using fluorescent markers for monitoring crystallization of e.g. proteins is disclosed by Pantoliano, which makes it obvious for a person of ordinary skill in the art to utilize this feature for crystallization monitoring in Weigl-Chayen's method.

Response to Arguments

10. Applicant's arguments filed 09/19/08 have been fully considered but they are not persuasive.

Regarding description of the invention as illustrated on Figure 5 and presented by the Applicants in their Remarks, the examiner does not believe that such description is

fully reflected in the pending claims. If the Applicants want to describe their invention in the manner similar to the one they presented in the Remarks, corresponding amendments should be made to the claims.

The examiner modifies rejections under 112, first and second paragraphs, with several issues added to the rejections, which should be addressed by the Applicants. It appears that the explanation for all issues is fully presented by the examiner in the present Office action. If the Applicants would like to discuss any issues for resolving problems with the claim language and/or enablement rejections, the Applicants are respectfully invited for a telephone interview with the examiner.

As to the rejection of the pending claims over the prior art, the examiner cannot agree with the Applicants regarding non-obviousness of the claimed method over the prior art. First, while Weigl teaches a homogenous mixing in the laminar flow, it is not apparent, as to what may prevent such homogenous mixing in the plugs (or droplets) which seems to be inherent for the small volumes of liquids. Therefore, separating the flow of homogenously mixed fluid from Weigl's method into plugs does not seem to teach away from Weigl's disclosure. The gradient is not required to be continues, and may be discontinues. Chayen specifically discloses preferences of having small volumes for the purpose of crystallization, so it appears that combining different conditions of crystallization disclosed by Weigl for the continuous laminar flow with providing small volumes of droplets or plugs separated by the immiscible liquid in the manner disclosed by Chayen leads to advantages of both methods. The advantages come from providing small volumes of fluids for controlled crystallization, as taught by Chayen, and as evidenced by the prior art submitted by the Applicants in the recent IDS, and from the flowing, rather than the stationary, system provided by Weigl. It appears that the claims should be amended for a more specific distinguishing between the combined prior art of Weigl and Chayen and the claimed method.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Yelena G. Gakh/
Primary Examiner, Art Unit 1797

11/8/2008